RENAL EFFECTS RISK MINIMISATION MATERIAL:

TRIVIRA (EFAVIRENZ/ EMTRICITABINE/ TENOFOVIR DISPOROXIL FUMARATE) FOR HIV-1 INFECTION IN ADULTS

Introduction

This brochure provides important advice on the management of potential renal effects of efavirenz/emtricitabine/tenofovir disporoxil fumarate (Trivira) in HIV-1 infection in adult patients aged 18 years and over, and on the dosing recommendations for efavirenz/emtricitabine/tenofovir disporoxil fumarate in this population.

Important Points to Consider:

- Check all patients' creatinine clearance before starting efaverinz, emitracitabine and tenofovir disporoxil fumarate therapy.
- During efaverinz, emitracitabine and tenofovir disporoxil fumarate therapy, renal function (creatinine clearance and serum phosphate) should be assessed regularly (after two to four weeks of treatment, after three months of treatment and every three to six months thereafter-in patients without renal risk factors) (see Table 1).
- In patients at risk for renal dysfunction a more frequent monitoring of renal function is required.
- Efaverinz, emitracitabine and tenofovir disporoxil fumarate should not be used in patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).
- Re-evaluate renal function within 1 week if serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min during efaverinz, emitracitabine and tenofovir disporoxil fumarate therapy.
- Interrupt treatment with efaverinz, emitracitabine and tenofovir disporoxil fumarate in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).
- Consider interrupting treatment with efaverinz, emitracitabine and tenofovir disporoxil fumarate in case of progressive decline of renal function when no other cause has been identified.
- Avoid concurrent or recent use of nephrotoxic medicinal products. If concomitant use is unavoidable, monitor renal function weekly.
- If efaverinz, emitracitabine and tenofovir disporoxil fumarate is co-administered with an NSAID, monitor renal function adequately.

Monitoring of renal function:

In clinical studies and post-marketing safety surveillance of efaverinz, emitracitabine and tenofovir disporoxil fumarate, rare events of renal failure (acute and chronic), renal impairment, acute tubular necrosis, nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus; and uncommon events of elevated creatinine, hypophosphatemia, proteinuria,

proximal renal tubulopathy (including Fanconi syndrome) have been reported. In some patients, events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) leading to bone abnormalities (infrequently contributing to fractures) have also been reported. Close monitoring of renal function is recommended for patients receiving efaverinz, emitracitabine and tenofovir disporoxil fumarate.

Efaverinz, emitracitabine and tenofovir disporoxil fumarate is not recommended for patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min). Treatment with efaverinz, emitracitabine and tenofovir disporoxil fumarate must be interrupted in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). The recommendations for monitoring renal function in patients without renal risk factors prior to and during efaverinz, emitracitabine and tenofovir disporoxil fumarate therapy are provided in Table 1. In patients at risk for renal dysfunction a more frequent monitoring of renal function is required.

Table 1: Monitoring of renal function in patients

	Prior to Efaverinz, Emitracitabine and Tenofovir disporoxil fumarate	**During 1st 3 months on Efaverinz, Emitracitabine and Tenofovir disporoxil fumarate**	**>3 months on Efaverinz, Emitracitabine and Tenofovir disporoxil fumarate**
Frequency	At baseline	At 2 to 4 weeks and 3 months	Every 3 to 6 months
Parameter	Creatinine clearance	Creatinine clearance and serum phosphate	Creatinine clearance and serum phosphate

If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving efaverinz, emitracitabine and tenofovir disporoxil fumarate, renal function must be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Treatment with efaverinz, emitracitabine and Tenofovir disporoxil fumarate must be interrupted in patients with confirmed creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l). Interrupting treatment with efaverinz, emitracitabine and tenofovir disporoxil fumarate should also be considered in case of progressive decline of renal function when no other cause has been identified.

Use of efaverinz, emitracitabine and tenofovir disporoxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If concomitant use is unavoidable, renal function must be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If efaverinz, emitracitabine and tenofovir disporoxil fumarate is co-administered with an NSAID, renal function should be monitored adequately.

Co-administration of atazanavir/ritonavir, lopinavir/ritonavir, ledipasvir/sofosbuvir with efaverinz, emitracitabine and tenofovir disporoxil fumarate is not recommended. It could potentiate renal disorders. Renal function should be closely monitored.

Darunavir/ritonavir should be used with caution in combination with efaverinz, emitracitabine and tenofovir disporoxil fumarate. Monitoring of renal function may be indicated, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.

Dosing recommendations for efaverinz, emitracitabine and tenofovir disoproxil

The recommended dose of efaverinz, emitracitabine and tenofovir disporoxil fumarate tablets for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over is 600mg/200mg/300mg (one tablet) once daily taken orally. Therapy should be initiated by a physician experienced in the management of HIV infection.

Please refer to the SPC of efavirenz/ emtricitabine/ tenofovir disporoxil fumarate for adjusting dose intervals in special populations (elderly patients, patients with renal impairment, patients with hepatic impairment, paediatric patients).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

The National Pharmacovigilance Centre
Saudi Food and Drug Authority
Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/

Saudi Amarox contact details:
Razan Almalki
Qualified Person for Pharmacovigilance
Al Jamiyah Street, Al Malaz
Riyadh code 12629, Saudi Arabia
E-mail: r.almalki@Amaroxpharma.com
Phone: +966 11 226 8850
Mobile: +966531215235

By reporting side effects, you can help provide more information on the safety of efavirenz/ emtricitabine/ tenofovir disporoxil fumarate.

Further information

For further information, please refer to the current Trivira SPC.